Docket No.: 273012012500
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of:
H. Andrew STRONG et al.

Application No.: 10/072,272

Filed: February 6, 2002

For: PHOTODYNAMIC THERAPY OF OCCULT AGE-RELATED MACULAR DEGENERATION

Confirmation No.: 1974

Art Unit: 1617

Examiner: Yong Soo Chong

REPLY BRIEF TO EXAMINER'S ANSWER

MS Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The Examiner's Answer in the present case was mailed on August 11, 2009, thus setting a date of October 11, 2009 for this Reply Brief. As October 11, 2009 fell on a Sunday, this Reply Brief is timely filed on the next business day, Tuesday, October 13, 2009.

Appellant appreciates the acknowledgement of the correctness of the status of claims, the status of amendments, the summary of the claimed subject matter and the grounds of rejection to be reviewed as well as the claims appendix, as set forth in the Examiner's Answer. Response has been provided herein to what seem to be new arguments raised in the Examiner's Answer.

It is assumed that this Reply Brief will be read in combination with the original Appeal Brief filed February 17, 2009 and the corrected Appeal Brief filed on May 26, 2009, and therefore only arguments in response to the Examiner's Answer are presented herein, with all other arguments from the Appeal Brief being incorporated by reference. Although not required, a listing of the claims is attached for the Board's convenience.

There is no *prima facie* case that claims 1, 2, 5-12, 14-18 and 20 are obvious over the TAP Report 1

Claims 1, 2, 5-12, 14-18 and 20 continue to be rejected as unpatentable under 35 U.S.C. § 103(a) as allegedly obvious over the TAP Report 1.

The Examiner's Answer acknowledges that the data in Table 5 of the TAP Report 1 shows that patients with >0 to <50% classic CNV (or >50 to <100% occult CNV) received no benefit from verteporfin therapy. (Examiner's Answer at page 8.) Appellants note that the percent of occult CNV lesions in these patients overlaps with the claimed range. Nevertheless, the Examiner maintains that because the subset of patients with $\geq$ 50% of classic CNV (or $\leq$ 50% occult CNV) received a large benefit from verteporfin treatment, one could infer that a patient with 50% occult CNV benefits from verteporfin therapy. Therefore, the Examiner concludes it would have been obvious to administer verteporfin therapy to a patient with 51% occult CNV using routine experimentation and optimization. (Examiner's Answer at page 8.)

The Examiner further states that because the standard of obviousness only requires a reasonable expectation of success, "it is obvious to experiment with a subgroup of patients on the outer limits of the claimed range of $\geq$ 50 to $\leq$ 100% occult CNV." (Examiner's Answer at page 8.)

There are at least two problems with the Examiner's position. First, patients having CNV lesions containing > 50% and < 100% occult CNV component (as claimed) were included in the

TAP Report 1 study, and as the Examiner has acknowledged, this subset of patients received no therapeutic benefit from verteporfin treatment. Thus, the Examiner's contention that the TAP Report 1 provides a reasonable expectation of success that such patients would benefit from verteporfin treatment is directly contradicted by the disclosure of the study itself that they did not, in fact, benefit from treatment. No rationale has been provided to justify this logical inconsistency in the Examiner's position.

Second, while the TAP Report 1 provides baseline characteristics for the study patients, including lesion size and visual acuity prior to treatment, nothing in the TAP Report 1 provides any means to correlate these characteristics with the percentage of occult component in the patient's CNV lesion. Thus, the TAP Report 1 provides neither a basis to select the claimed subpopulation nor a reasonable expectation that the claimed subpopulation would benefit from treatment. The Examiner's position that the present invention would have been obvious at the time of the present invention improperly relies on hindsight reasoning based on the Appellant's discovery that patients having lesions containing > 50% and < 100% occult CNV component in combination with small lesion size and/or poor visual acuity prior to treatment benefited from photodynamic therapy.

The Examiner's reliance on page 1339 on TAP Report 1 as allegedly rendering obvious the upper limit of the claimed range (which the Examiner's Answer at page 8 characterizes as 99% occult CNV) also appears misplaced. The contention that the TAP Report 1 teaches that 'the subgroup with no classic CNV (100% occult CNV) had a large treatment benefit" ignores the remainder of the sentence, which reads in full: "In contrast, the subgroup with no classic CNV (100% occult CNV) had a large treatment benefit; however, the number of patients in this subgroup

was small and did not meet the eligibility criteria from the trials according to the Photograph Reading Center's interpretation of the angiogram." (See TAP Report 1 at page 1339.)

Thus, the Appellant submits that, contrary to the Examiner's contention, one of skill in the art would not have had a reasonable expectation of success based on the data from a small group of patients who did not meet the study criteria. Moreover, even in if such patients were selected, it would not have led to the invention as claimed, which requires recognition that the additional features of small lesion size and/or poor visual acuity prior to treatment be included in combination with the percent occult component to select the treatment subpopulation.

The methods of the invention provide unexpected results that rebut any *prima facie* case of obviousness

The Examiner's Answer also rejects as unpersuasive the Appellant's evidence that any *prima facie* case of obviousness is rebutted by a showing of unexpected results. The Examiner takes the position that "Appellant has not established a case of unexpected results when compared to the cited prior art and that is commensurate with the scope of the claims. The data pointed to in Appellant's specification (43.8% difference between the verteporfin and placebo groups) is not a clear and convincing case of unexpected results."

The only independent claim, claim 1, is directed to a PDT method for treating a subpopulation subjects having occult CNV lesions. The method requires selecting a subject with an occult CNV lesion comprising an occult component of >50% and <100% of the lesion and assessed as having either (a) a small lesion with a size less than 5 disc areas, or (b) poor visual acuity of less than 65 letters prior to treatment, or both (a) and (b).

The data in Table 2 of the instant specification shows the impact of the baseline visual acuity score and lesion size on the outcome of treatment with verteporfin PDT in patients having occult

CNV lesions 24 months after the initial treatment. (See Specification at paragraph 163, Table 2.) The data is presented as the difference in the percentage of subjects losing less than 15 letters (or less than 30 letters) of visual acuity for verteporfin treated patients versus those receiving placebo. Thus, the larger the percent difference, the more benefit the patients received from treatment (i.e., the larger the reduction in the loss in visual acuity upon treatment).

The data provided in Table 2 of the specification demonstrate that occult CNV patients having the additional criteria of poor visual acuity at baseline and/or small lesion size achieved significantly improved visual acuity outcomes relative to placebo at 24 month after initial treatment. Moreover, this data demonstrates that these patients had a significantly improved outcome relative to the patients with >0 to <50% classic CNV (or >50 to <100% occult CNV) in the TAP Report 1, who received no benefit from verteporfin therapy at 12 months after initial treatment.

As disclosed in Table 2 of the instant specification, for all subjects having visual acuity at baseline less than 65 letters and lesion size less than or equal to 4 disc areas, the difference in the percent of subjects receiving verteporfin versus placebo who lost less than 15 letters was 43.8%. (See specification, paragraph 163, Table 2, row 2.) For subjects having visual acuity at baseline less than 65 letters and lesion size greater than or equal to 4 disc areas, the difference in the loss of less than 15 letters between the treatment and placebo groups was 21.5%. (See specification, paragraph 163, Table 2, row 3.) Subjects having lesion size less than or equal to 4 disc areas and visual acuity of greater than or equal to 65 letters at baseline showed a smaller improvement, with a difference in the loss of less than 15 letters between treatment and placebo groups of 12.5%. (See specification, paragraph 163, Table 2, row 5.) No improvement in the loss of visual acuity was observed 24 months after verteporfin treatment for occult CNV patients having visual acuity greater

than or equal to 65 letters at baseline and a lesion size of greater than or equal to 4 disc areas; indeed, verteporfin treatment appeared negatively correlated with visual acuity in these subjects. (See specification, paragraph 163, Table 2, row 6.)

By comparison, the TAP Report 1 discloses subgroup analyses for the primary outcome of visual acuity at 12 months for different subpopulations. As previously noted by the Appellants, the TAP Report 1 discloses that "[n]o statistically significant differences in visual acuity were noted when the area of classic CNV was more than 0% but less than 50% of the area of the entire lesion." (See TAP Report 1, page 1329 at "Results".) The TAP Report 1 discloses that the "subgroup analysis showed a large treatment benefit when the lesion was predominantly classic CNV (i.e., the area of classic CNV occupied $\geq$ 50% of the area of the entire lesion) at baseline" with 33% of verteporfin treated eyes showing a loss of 15 or more letters at the 12 month examination, versus 61% of the patients receiving placebo. (See TAP Report 1 at page 1338.) Appellants note that this difference, which the study's authors characterize as "a large treatment benefit," is 28%, significantly less than the 43.8% difference between the treatment and placebo groups in occult CNV patients having poor visual acuity and small lesion size described in the present application, and comparable to the 21.5% difference in occult CNV patients having poor visual acuity, but lesion size $\geq$ 4 disc areas in the instant specification. In view of the characterization of the results in the TAP Report 1 as "a large treatment benefit" by the study's authors, it is unclear to the Appellants what level of improvement the Examiner would consider clear and convincing evidence of unexpected results if the data provided in the instant specification is not.

Moreover, the present application discloses the improvement in visual acuity outcomes at 24 months after initial treatment, so that the subjects' visual acuity has had an additional 12 months

post-treatment to diminish versus the 12 months post-treatment determination disclosed in the TAP Report 1. This data suggests that not only was there a significant improvement in the loss of visual acuity upon verteporfin treatment, but that the improvement was maintained for at least 24 months post-treatment.

Conclusion

The present invention provides methods for treating a sub-population of occult CNV patients falling within a group for whom the TAP Report 1 teaches that PDT treatment with verteporfin is ineffective. The recognition that a specific sub-population of patients can be beneficially treated is unexpected in view of the teachings in the cited documents. The TAP Report 1, alone or in combination with Zeimer, provides no guidance that would lead to the selection and treatment of the claimed sub-population, and the cited documents would not provide a person of skill in the art with either a reasonable expectation of success or any motivation or other rationale to practice the instantly claimed methods. Moreover, the present invention provides unexpected results sufficient to rebut any *prima facie* case of obviousness.

Appellants respectfully request that the rejections be withdrawn and claims 1, 2 and 5-20 be passed to issue on an expedited basis.

An Oral Hearing is requested.

The Assistant Commissioner is hereby authorized to charge any additional fees under 37 C.F.R. § 1.17 that may be required by this Reply Brief, or to credit any overpayment, to **Account No. 03-1952**.

Respectfully submitted,

Dated: October 13, 2009

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CLAIMS APPENDIX

1. (previously presented): A method for treating an occult choroidal neovascular (CNV) lesion in a subject comprising

selecting a subject with an occult CNV lesion comprising an occult component of >50% and <100% of the lesion and assessed as having either (a) a small lesion with a size less than 5 disc areas, or (b) poor visual acuity of less than 65 letters prior to treatment, or both (a) and (b); and

providing photodynamic therapy (PDT) to the subject having said CNV lesion.

2. (original): The method of claim 1 wherein said subject was assessed by determining the size of said lesion and/or determining the best corrected visual acuity of the subject.

3-4. (canceled)

5. (previously presented): The method of claim 1 wherein the small lesion has a size less than 4 disc areas.

6. (previously presented): The method of claim 1, wherein said occult CNV lesion is in a subject afflicted or diagnosed with age-related macular degeneration (AMD).

7. (original): The method of claim 1 wherein said PDT comprises the administration of a photosensitizer (PS).

8. (original): The method of claim 7, wherein the PS is administered at a concentration ranging between about 2 to 8 mg/m^2 (PS/body surface area of subject).

9. (original): The method of claim 8, wherein the PS is administered at a concentration of 6 mg/m^2.

10. (original): The method of claim 9, wherein the PS is a green porphyrin.

11. (original): The method of claim 10, wherein the green porphyrin is selected from BPD-DA, BPD-DB, BPD-MA, BPD-MB, EA6, and B3.

12. (original): The method of claim 11, wherein the green porphyrin is BPD-MA.

13. (original): The method of claim 10, wherein the PS is coupled to a specific binding ligand.

14. (original): The method of claim 7, wherein the PS is formulated with a carrier.

15. (original): The method of claim 14, wherein the formulation is selected from the group consisting of a liposome, emulsion, or aqueous solution.

16. (original): The method of claim 1, wherein said PDT comprises irradiation with electromagnetic radiation containing wavelengths in the visible light spectra.

17. (original): The method of claim 16, wherein the irradiation provides between 12.5 J/cm^2 and 100 J/cm^2.

18. (original): The method of claim 17, wherein said irradiation occurs between 5 to 30 minutes after administration of a photosensitizer.

19. (original): The method of claim 7, wherein the PS is administered at a concentration ranging between about 10 μg/kg to 100mg/kg (PS/body weight of subject).

20. (previously presented): The method of claim 1, wherein a resulting loss of visual acuity is less with treatment than without treatment.

21. (withdrawn): The method of claim 11, wherein the green porphyrin is EA6.